Form PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (Rev. 11-2000)

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

Attorney's Docket Number	
49276-262679	
U.S. Application No. (if known, see 37 CFR 1.5)	
09/914241	
International Application No.	International Filing Date
PCT/EP00/01497	**24 February 2000**
Priority Date Claimed	
26 February 1999	

Title of Invention

HEMOCOMPATIBLE SURFACES AND METHOD FOR PRODUCING SAME

Applicant(s) for DO/EO/US

Horres, Roland and
Hoffmann, Michael

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)). This submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The U.S. has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    Filing Fee Check for US$ 495;
    Postcard

Express Mail Label No. EL910716320US Date: 24 August 2001

U.S. Application No. (if known, see 37 CFR 1.5)	International Application No.	Attorney's Docket Number
09/914241	PCT/EP00/01497	49276-262679

21. ☒ The following fees are submitted: CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..$1000.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....$860.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$710.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4).....$690.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4).....$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 860.00
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$ 130.00
Claims	Number Filed	Number Extra	Rate	
Total claims	1 - 20 =	0	x 18.00	$ 0
Independent Claims	1 - 3 =	0	x 80.00	$ 0
Multiple Dependent Claims (if applicable)			+ 270.00	$
TOTAL OF ABOVE CALCULATIONS =				$ 990.00
☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			-	$ 495.00
SUBTOTAL =				$
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$
TOTAL NATIONAL FEE =				$
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property			+	$
TOTAL FEES ENCLOSED =				$ 495.00
			Amount to be refunded:	$
			charged:	$

a. ☒ A check in the amount of $ 495.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 11-0855 in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 11-0855. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form**. Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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John K. McDonald, Ph.D.
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DUPLICATE

JC05 Rec'd PCT/PTO 24 AUG 2001

U.S. Application No (if known, see 37 CFR 1.5)	International Application No	Attorney's Docket Number
09/937421	PCT/EP00/01497	49276-262679

21. ☒ The following fees are submitted: CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..$1000.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....$860.00

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International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4).....$100.00

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Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$ 130.00	
Claims	Number Filed	Number Extra	Rate		
Total claims	1 - 20 =	0	x 18.00	$ 0	
Independent Claims	1 - 3 =	0	x 80.00	$ 0	
Multiple Dependent Claims (if applicable)			+ 270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 990.00	
☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. -				$ 495.00	
SUBTOTAL =				$	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 495.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 495.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 11-0855 in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

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John K. McDonald, Ph.D.
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Patents

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
DESIGNATED/ELECTED OFFICE

In re Application of:

HORRES, ROLAND AND HOFFMANN, MICHAEL

Serial No.: **Not Yet Assigned**

Filed: **24 August 2001**
National Phase of PCT/EP00/01497
Filed February 24, 2000

For: **HEMOCOMPATIBLE SURFACES AND METHOD FOR PRODUCING SAME**

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231

Attn: DO/EO/US

Sir:

Prior to examination of the present application, please enter the following amendments to the specification and claims.

In The Specification:

On page 1, after the title please insert the following:

PRIOR RELATED APPLICATION

The present application is a National Phase of PCT/EP00/01497, filed February 24, 2000, which claims priority to German Patent Application No. 199 08 318.5, filed February 26, 1999.

Express Mail Label No.: **EL910716320US**

Date of Deposit: **24 August 2001**

In The Claims:

Please cancel Claims 1 through 14 and insert new Claim 15.

15. (New) A hemocompatible surface, wherein the hemocompatible surface comprises a material on or in the hemocompatible surface, and the material comprises an artificial compound, a natural organic compound, an inorganic compound or a mixture thereof, and a constituent of an outer layer of a blood cell, a mesothelial cell or a combination thereof.

By this amendment, Claims 1-14 are cancelled and Claim 15 is added. There is now one claim pending, Claim 15.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855.

Respectfully submitted,

John K. McDonald, Ph.D.
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HEMOCOMPATIBLE SURFACES AND METHOD FOR PRODUCING SAME

The present invention concerns hemocompatible surfaces which are characterized in that constituents of the outer layers of blood cells and/or mesothelial cells are applied and/or incorporated onto and/or into the surfaces of materials.

The present invention further concerns a process for manufacturing hemocompatible surfaces and their use in extensive fields of health, in medicine, dentistry, surgery, cosmetics and/or fields having direct contact with blood, tissue and/or other body fluids.

In the case of vertebrates, blood coagulation is a complex process which temporarily protects against critical losses of blood in the case of injury. The blood coagulation system is activated, among other things, by contact with unphysiologic, i. e., 'exogenous' substances in this case. Substances which actively suppress the blood coagulation system are also referred to as anti-thrombogenic. Substances which do not even activate the blood coagulation system are defined as non-thrombogenic.

Especially in the case of invasive operations, the activation of the blood coagulation system is a serious problem for the patient. This is, in particular, the case for people dependent on implants, such as intra-coronary stents, cardiac valves, prosthetic devices, artificial vascular systems, dialysers, or oxygenators, catheters, biosensors etc.. Contact with surgical suture materials can also cause problems.

Until now, in order to prevent the formation of critical occlusions of vessels (thrombi), the blood coagulation system has been deactivated or actively suppressed. This is normally done by the administration of anti-thrombogenic medicine, so-called anticoagulants, which however, have many serious side effects for the patient, such as thrombocytopenia, nausea, vomiting, hair loss, haemorrhagic skin gangrenes, higher tendency to bleed etc.. Moreover,

if intra-coronary stents or cardiac valves are used, even the complete medicamentous suppression of blood coagulation often does not sufficiently prevent the formation of thrombosis, which can cause death.

In extensive fields of health, in medicine, dentistry, surgery, cosmetics or, in general, fields having contact with blood and/or other body fluids in invasive operations, it is therefore very important to avoid the above-mentioned serious side effects caused by anticoagulants.

From prior art, various processes are known which are intended to make unphysiologic 'foreign surfaces' more blood compatible (hemocompatible) or histocompatible by coating with different substances.

DE 28 31 360, for example, describes a process for coating a surface of a medical article with a substance (heparin) which actively suppresses the coagulation system, i. e., is anti-thrombogenic. Said substance, however, has the disadvantage of serious side effects for the patient, as already mentioned before by way of example.

In DE 44 35 653, materials are coated with a thin coat of lacquer of polymers into which medicinal agents can be additionally incorporated, wherein said coat of lacquer permanently degrades in the body and is thus released. The disadvantages of this method are, first of all, that because of the permanent degradation of the coating only a temporally limited effect can be achieved. Secondly, due to the permanent separation of particles of lacquer, there is a high danger of the formation of thrombosis, which can cause embolisms.

DE 196 30 879 exclusively uses chemically modified derivatives of polysaccharides for coating substrates. There are various disadvantages regarding this process, ranging from excessive preparative expenses to synthesis steps including many stages, a wide range of undesirable side reactions and poor exploitation up to worse properties of the derivatives in every respect when compared to commercially available anti-thrombogenic substances such as heparin.

Verhagen et al. (British Journal of Heamatology, 1996, 95: 542-549) describes the use of entire living cells of the endothelium or the mesothelium for the colonisation of implants. The disadvantage of using entire cells is the fact that, due to specific cell surface proteins, immune reactions are

caused, which cause rejection reactions against the coated implants for the patients. Substances inducing such an immune reaction are also called immunogenic. To prevent a rejection by immune reactions, it is necessary that exclusively cell material of the patients themselves is used in this process. This is a further disadvantage because considerable time and costs are involved in culturing these cells. A further problem regarding the use of entire cells are the high shearing forces to which these cells are subjected in the blood stream. This leads to an increased degradation of the cells at the surfaces, which has a negative effect on the durability of the coated implants.

Also WO 93/01843, WO 95/29712 and DE 195 05 070 describe the use of entire living endothelial cells for coating unphysiologic materials or the use of substances contributing to the growing of living endothelial cells on artificial materials. But also in these cases, all processes are based on the cultivation of living endothelial cells, which involves the disadvantages mentioned above with respect to the time required and the cost involved or the considerable limitation that the coated material cannot be used universally, but has to be produced separately for every patient.

From patent specification DE 36 39 561, the production of substrates coated with the specific endothelial cell surface proteopolysaccharide HS-I is known. The disadvantage of the process is the fact that also in this case considerable amounts of endothelial cells of the patients themselves are required for isolating these components. This requires for every patient a time-consuming and cost-intensive cultivation of his endogenous endothelial cells, which, in addition, is followed by a costly preparation of the proteopolysaccharide HS-I. Therefore, the mass production of HS-I and thus an economic use of this process for coating implants cannot be realized.

Accordingly, the object of the present invention is to provide blood compatible (hemocompatible) or histocompatible surfaces which do not show the disadvantages mentioned above and are, at the same time, suitable for mass production.

According to the invention, the object is solved by means of hemocompatible surfaces characterized in that they contain as the materials artificial and/or natural organic and/or inorganic compounds and/or mixtures

thereof and/or materials having contact with blood and/or other body fluids in invasive operations and/or animal organs and/or organ parts, and constituents of the outer layer of blood cells and/or mesothelial cells are applied and/or incorporated onto and/or into the surface of said materials.

The hemocompatible surfaces of the invention thus substantially imitate the outer surface of blood and/or mesothelial cells, synonymous with the imitation of the natural surface of non-thrombogenic cells and/or tissue.

The blood coagulation system is therefore neither activated nor actively suppressed by the hemocompatible surfaces. Accordingly, a blood coagulation which is, for example, caused by secondary injuries (cuts or the like) can take place in a completely natural and undisturbed way.

A further advantage of the present invention is the fact that an adhesion of cells such as thrombocytes on the hemocompatible surfaces according to the invention does not occur. This is desired by the invention because the risk of the formation of thrombi, i. e., the danger of a thrombosis (embolism) for the patient treated is minimized thereby. The hemocompatible surfaces according to the invention do no cause any side effects.

According to the invention, the hemocompatible surfaces are further characterized by the fact that they are non-thrombogenic in the long term. This means that their advantageous properties are not used up in the course of time, which is, for example, the case for pharmaceutically active systems (for example release system). For this reason, the surfaces according to the invention are also suitable for permanent use, so that additional burdening and risks for the patients by repeated invasive operations for renewing the implants are minimized.

According to the invention, the hemocompatible surfaces contain as the materials artificial and/or natural organic and/or inorganic compounds and/or mixtures thereof and/or materials having contact with blood and/or other body fluids in invasive operations and/or animal organs and/or organ parts, and constituents of the outer layers of blood cells and/or mesothelial cells are applied and/or incorporated onto and/or into the surfaces thereof.

In the sense of the invention, materials refer to any materials which, according to the invention, are suitable for being loaded with cell constituents. Also comprised are any materials which can come into contact with

blood and/or body fluids during invasive operations or in connection with respective postoperative care.

Organic compounds refer, for example, to synthetically produced or naturally occurring high-molecular substances and their derivatives. Examples for these are, among others, any kinds of plastics, elastomers, silicones or fibrous substances. They include, for example, polyethylenes (PE), polyvinyl chlorides (PVC), polyurethanes (PUR), polyamides (PA), phenoplasts (PF), aminoplasts, polystyrene, polyester, resins, silicones, rubbers, man-made fibers, cellulose fibers, cellulose membranes, protein fibers, collagens, as well as derivatives thereof or combinations thereof. Further comprised according to the invention are mixtures of these polymers, so-called polymer blends.

In a special embodiment of the present invention, as materials, the hemocompatible surfaces according to the invention can include animal organs, organ parts or vascular systems. They can, for example, be cardiac valves and/or vascular systems, wherein pigs or cattle are especially suitable as sources.

Examples for inorganic compounds included by the hemocompatible surfaces according to the invention are metals, metal oxides, alloys or ceramics, glasses and/or minerals as well as derivatives thereof or any possible combinations and/or mixtures thereof. According to the invention, any possibilities of combination of materials are possible. The examples explain the present invention in greater detail, but are not intended to be limiting.

According to the invention, constituents of the outer layers of blood cells and/or mesothelial cells are incorporated and/or applied into and/or onto the surface of the materials.

In one embodiment of the present invention, the hemocompatible surfaces include in and/or on the surface of materials glycoproteins, preferably glycophorins. Said glycophorins are, among other things, characterized by non-thrombogenic properties, and are therefore excellently suitable for making hemocompatible surfaces according to the invention.

The glycophorins of the outer layer of the erythrocytes, determine, among other things, the blood group to which a human being belongs. Analogously to the different blood groups A, B, AB and 0, the corresponding

erythrocytes contain glycophorin A, glycophorin B or glycophorin 0 or respective mixtures thereof.

A possible immunological response by cross-reactions of blood groups which are not compatible with each other, i. e., clotting of blood (coagulation) can be avoided in a simple way by matching with respect to the blood group of the patient treated and the glycophorins applied and/or incorporated onto and/or into the surfaces of materials of the hemocompatible surfaces of the invention which are intended for application, wherein said matching is carried out before the invasive operation. Respective blood tests are common practice in laboratories and, accordingly, are carried out routinely. Provided that the blood-group compatibility is observed, hemocompatible surfaces containing glycophorin can thus also be used universally, i. e., they are not restricted to only one patient.

The present invention further concerns hemocompatible surfaces including on and/or in the surfaces of the materials oligosaccharide, polysaccharide and/or lipid portions of the glycoproteins, glycolipids and/or proteoglycans from the outer layer of blood cells and/or mesothelial cells.

In a further embodiment of the present invention, the hemocompatible surfaces contain glycosphingolipids on and/or in the surfaces of the materials.

The hemocompatible surfaces of the present invention further can contain as the oligosaccharide or polysaccharide portions of the proteoglycans hyaluronic acids, chondroitin sulfates, dermatan sulfates, heparan sulfates, keratan sulfates or mixtures thereof. In a preferred embodiment of the present invention, the hemocompatible surfaces contain heparan sulfate of the erythrocyte plasma membrane of animal and/or human origin.

The hemocompatible surfaces according to the invention do not show any side effects, which are caused, for example by chemically or pharmaceutically active coatings.

The above-mentioned constituents of the blood and/or mesothelial cells are non-immunogenic cell constituents. Accordingly, the hemocompatible surfaces according to the invention are characterized in that they are also non-

immunogenic. This means they do not cause an immune reaction for the patient, which minimizes the danger of rejection of the hemocompatible surfaces.

According to the invention, the hemocompatible surfaces are non-thrombogenic and/or non-immunogenic.

A further advantage is the fact that almost no degradation takes place at the hemocompatible surfaces due to the firm attachment of the non-thrombogenic constituents of the outer layers of the blood and/or mesothelial cells on the materials according to the invention. The danger of the formation of embolisms by thrombosis is thus minimized. Furthermore, there is no accumulation of cells such as thrombocytes on the hemocompatible surfaces according to the invention. This also minimizes the danger of thrombosis.

The subject matter of the invention further comprises a process for the production of the hemocompatible surfaces according to the invention, wherein glycophorins, oligosaccharide, polysaccharide and/or lipid portions of the glycoproteins, glycolipids and/or proteoglycans from the outer layer of blood cells and/or mesothelial cells are isolated, and these cell constituents are applied and/or incorporated onto and/or into the surfaces of materials of artificial and/or natural organic and/or inorganic compounds and/or mixtures thereof and/or materials having contact with blood and/or other body fluids in invasive operations and/or animal organs and/or organ parts by physical or chemical bonding.

According to the invention, the constituents of the outer layer of blood cells are isolated from whole blood and/or from cell fractions obtained therefrom of human or animal origin. This means that the cell constituents are isolated from erythrocytes, leucocytes and/or thrombocytes or mixtures thereof. Preferred are mixtures of erythrocytes and leucocytes. Especially preferred are erythrocytes.

The constituents of the outer layer of mesothelial cells are, according to the invention, isolated from omentum, peritoneum and/or inner organs.

A cheap and easily accessible source for these starting materials can be waste from slaughtering, for example.

The isolation of the constituents of the outer layer of the blood cells, mesothelial cells or of the tissue rich in mesothelial cells is carried out in a common manner in this case. The following processes or combinations thereof are, for example, possible: comminution, extraction, filtration, precipitation, gel filtration, ion exchange chromatography, affinity chromatography, electrophoresis, enzymatic or chemical degradations, drying, dissolution, dialysis, ultrafiltration etc..

According to the invention, for applying and/or incorporating the cell constituents onto and/or into the surface of the materials, a chemical immobilization, photoimmobilization, adhesion, drying process or a combination thereof is carried out. Covalent, ionic, secondary valence or electrostatic or adhesive bonds or combinations thereof can be formed between the constituents of the outer layer of the cells and the surfaces of the materials in this case. Preferably, the application or integration of the constituents of the outer cell layer onto/into the surfaces of materials is carried out by covalent bonds.

A special advantage of the present invention is the fact that the production process according to the invention combines enormous economical advantages compared to the processes known until now, and, accordingly, the hemocompatible surfaces according to the invention are suitable for mass production.

The reasons for this are, for example, that, according to the invention, cell constituents and not living cells are used, that no endogenous (endothelial) cells of the patient must be used, that the starting material for the isolation of said cell constituents is cheap and available in big amounts (waste from slaughtering), so that cell cultivation, which is very time-consuming and cost-intensive, is not necessary. A further advantage of the hemocompatible surfaces according to the invention is the fact that they can be used universally and are not restricted to the use for only one patient. Above all, in the case of emergency operations, this advantage is essential for a patient's life.

There is a wide range of fields of applications in which the present invention can be used. The present invention concerns the use of hemocompatible surfaces in extensive fields of health, in medicine, dentistry, surgery or cosmetics

and/or in fields having contact with blood, tissue and/or other body fluids during invasive operations.

In the following, the invention is described in greater detail with reference to the examples, which, however, are not intended to be limiting:

1.) ISOLATION OF ERYTHROCYTE PLASMA MEMBRANE HEPARAN SULFATE:

One liter of erythrocytes which have been washed free of serum are suspended in 1 liter of a 0.154 molar phosphate buffer pH 7, and 1 U/ml papain is added. After 2 hours of incubation at 56°C, centrifuging takes place at 3000 g for 20 minutes, and, subsequently, the supernatant is decanted. In this supernatant, 100 ml of DEAE Sepharose CL-6B ion exchanger gel of the company Pharmacia Biotech are suspended. The gel loaded in this way is still washed three times in a 0.1 molar saline solution and filled into a chromatographic column. The elution takes place by means of a linear sodium chloride gradient in the range of 0.1 to 0.8 moles/l over an entire elution volume of 2 liters. 200 fractions of a volume of 10 ml each are collected. The fractions showing a positive color reaction with dimethylmethylene blue (DMMB) of the company Fluka according to the method described by Chandrasekhar et al (Analytical Biochemistry, 161 (1987): 130-108) are united. The solution of the collected fractions is narrowed down at 26.7 hPa (20 torrs) and 40°C and dialysed against water. The dialysate is set to a volume of 100 ml and a concentration of 0.03 moles/l of sodium acetate, 0.073 moles/l of tris (tris(hydroxymethyl)aminomethane of the company Fluka) and pH 8.0, 1 U of chondroitinase ABC is added, and incubation takes place at 37°C for 15 hours. After dialysing against water and narrowing down under water jet vacuum, the resulting solution is again applied onto a column with 100 ml of DEAE Sepharose CL-6B of the company Pharmacia Biotech. and eluted as described before. The DMMB positive gradient fractions are dialysed, narrowed down under water jet vacuum to a volume of 1 ml and chromatographed on a column for preparative gel filtration (60 cm x 2 cm) using a Sephacryl S-300 gel (Pharmacia Biotech.). 60 fractions of a volume of 2 ml each are collected, detected with DMMB, and the positive fractions are united. After repeated

dialysis and lyophilisation, the purified erythrocyte plasma membrane heparan sulfate will be obtained.

2.) ISOLATION OF LEUCOCYTE SURFACE PROTEO-CHONDROITIN SULFATE:

One liter of citrate blood is centrifuged for 10 minutes in a centrifuge with a swing-out rotor at 3000 g, and the supernatant plasma is drawn off. The cell sediment is mixed with 2 liters of a 1% ammonium oxalate solution cooled to 4°C, and is incubated for 30 minutes at the same temperature. After 5 minutes of centrifugation at 500 g, the red supernatant is discarded and the pellet is suspended in 2 liters of a 1% ammonium oxalate solution cooled to 4°C, centrifuged for 5 minutes at 500 g, and the washing process as described above is repeated two more times. The supernatant which is now colorless is discarded, and the washed cell sediment (yield: 12×10^7 - 10×10^9 cells in 2 liters of triton X-100 buffer (0.5 % triton X-100, 10 mM tris-HCl, 150 mM NaCl, pH 8) is lysed for 2 hours at 25°C under constant stirring. The detergent extract is centrifuged for 60 minutes at 10,000 g, decanted, and in the supernatant, 10 ml of DEAE Sephadex A50 ion exchanger gel of the company Pharmacia Biotech are suspended and sedimentated. The gel loaded in this way is still washed three times in a 0.1 molar saline solution and filled into a chromatographic column. The elution of the column takes place by means of a linear sodium chloride gradient in the range of 0.1 to 0.8 moles/l over an entire elution volume of 2 liters. 100 fractions of a volume of 2 ml each are collected, and the fractions showing a positive color reaction with dimethylmethylene blue (DMMB) of the company Fluka are united. The solution is narrowed down at 26.7 hPa (20 torrs) and 40°C and dialysed against water. The dialysate is set to a volume of 100 ml and a concentration of 0.1 mmoles/l of calcium acetate and 0.1 moles/l of sodium acetate, titrated with acetic acid to pH 7, 1 U of heparinase I, heparinase II and heparinase III are added, respectively, and incubation takes place at 37°C for 15 hours.

After dialysing against water and narrowing down under water jet vacuum, the resulting solution is again applied onto a column with 10 ml of DEAE Sephadex A50 of the company Pharmacia Biotech. and eluted as

described above. The DMMB positive gradient fractions are dialysed, narrowed down under water jet vacuum to a volume of 1 ml and chromatographed on a column for preparative gel filtration (60 cm x 2 cm) using a Sepharose CI-4B gel of the company Pharmacia Biotech. 60 fractions of a volume of 2 ml each are collected, detected with DMMB, and the positive fractions are united. After repeated dialysis and lyophilisation, the cleaned leucocyte surface proteo-chondroitin sulfate will be obtained.

3.) ISOLATION OF HEPARAN SULFATE/CHONDROITIN SULFATE MIXTURE FROM OMENTUM:

One kilogram of fresh bovine omentum is washed with a 0.9 % NaCl solution, freeze-dried, ground, and degreased with 1 liter of acetone by stirring over night at room temperature. After filtering and drying, the resulting powder is suspended in a 6 molar urea solution and stirred over night at room temperature. After centrifugation at 3000 g for one hour, the mucous supernatant is decanted, cooled to 4°C, mixed with the same volume of 1 molar NaOH of a temperature of 4°C, and incubated for 15 hours at 4°C. Subsequently, neutralization with dilute HCl, dialyzing against water and centrifugation for 1 hour at 3000 g takes place, and the supernatant is decanted. In the supernatant, 100 ml of DEAE Sepharose CL-6B ion exchanger gel of the company Pharmacia Biotech are suspended and sedimentated. The gel loaded in this way is still washed three times in a 0.1 molar sodium chloride solution and filled into a chromatographic column. The elution of the column takes place by means of a linear sodium chloride gradient in the range of 0.1 to 0.8 moles/l over an entire elution volume of 2 liters. 200 fractions of a volume of 10 ml each are collected, and the fractions showing a positive color reaction with dimethylmethylene blue (DMMB) are united. The solution is narrowed down at 26.7 hPa (20 torrs) and 40°C and dialyzed against water. Under water jet vacuum, again, narrowing down takes place to a volume of 5 ml, and chromatographing is carried out on a column for preparative gel filtration (60 cm x 5 cm) using a Sephacryl S-300 gel of the company Pharmacia Biotech.. 60 fractions of a volume of 10 ml each are collected, detected with DMMB, and the positive fractions are united. After

repeated dialysis and lyophilisation, the purified mesothelial-cell-surface glycosamino glycan mixture will be obtained.

4.) ISOLATION OF MESOTHELIAL CELL SURFACE CHONDROITIN SULFATE FROM TISSUES RICH IN MESOTHELIAL CELLS:

One kilogram of fresh bovine kidneys are washed with a 0.9 % NaCl solution, freeze-dried, ground, and degreased with 1 liter of acetone by stirring over night at room temperature. After filtering and drying, the resulting powder is suspended in a 4 molar guanidinium chloride solution and stirred over night at room temperature. After centrifugation at 3000 g for one hour, the mucous supernatant is decanted, cooled to 4°C, mixed with the same volume of 1 molar NaOH of a temperature of 4°C, and incubated for 15 hours at 4°C. Subsequently, neutralization with dilute HCI, dialyzing against water and centrifugation for 1 hour at 3000 g takes place, and the supernatant is decanted. In the supernatant, 100 ml of DEAE Sephacel ion exchanger gel are suspended and sedimentated. The gel loaded in this way is still washed three times in a 0.1 molar sodium chloride solution and filled into a chromatographic column. The elution of the column takes place by means of a linear sodium chloride gradient in the range of 0.1 to 0.8 moles/l over an entire elution volume of 2 liters. 200 fractions of a volume of 10 ml each are collected, and the fractions showing a positive color reaction with DMMB are united. The solution is narrowed down at 26.7 hPa (20 torrs) and 40°C and dialyzed against water. The dialysate is set to a volume of 100 ml and a concentration of 0.1 mmoles/l of calcium acetate and 0.1 moles/l of sodium acetate, titrated with acetic acid to pH 7, 1 U of heparinase I, heparinase II and heparinase III are added, respectively, and incubation takes place at 37°C for 15 hours.

After dialysing against water and narrowing down under water jet vacuum, the resulting solution is again applied onto a column with 10 ml of DEAE Sephacel and eluted as described before. The DMMB positive gradient fractions are analysed, narrowed down under water jet vacuum to a volume of 1 ml and chromatographed on a column for preparative gel filtration (60 cm x 5 cm) using a Sephacryl S-300 gel. 60 fractions of a volume of 10 ml each are collected, detected with DMMB, and the positive fractions are united. After

repeated dialysis and lyophilisation, the purified mesothelial cell surface chondroitin sulfate will be obtained.

5.) IMMOBILIZATION OF MESOTHELIAL CELL SURFACE CHONDROITIN SULFATE WITH (N-CYCLOHEXYL-N'-2-MORPHOLINOETHYL)CARBODIIMIDE METHYL TOSYLATE (CME-CDI) ONTO FUNCTIONAL CELLULOSE SURFACES:

100 mg of cellulose membrane are added to a 2 per cent solution of 3-aminopropyl-triethoxy silane in ethanol/water (50:50) and stirred for 24 hours at 45°C. Subsequently, the membranes are washed with a lot of water and are dried. The membranes treated in this way are immersed into a solution of 1 mg of mesothelial cell surface chondroitin sulfate in 80 ml of 0.1 molar 2-(N-morpholino)ethane sulfone acid buffer pH 4.75. Over a period of 6 hours at 4°C, 200 mg of (N-cyclohexyl-N'-2-morpholinoethyl)carbodiimide methyl tosylate (CME-CDI) of the company Sigma are added in portions of 10 mg and are further stirred over night at 4°C. Subsequently, stirring for 2 hours in a 4 molar NaCl solution, washing with a lot of water and drying in the fresh air takes place.

6.) CNCI IMMOBILIZATION OF SPHINGOGLYCOLIPID ONTO GLASS:

A glass, for example a cover glass for microscopy, is stirred for 6 hours in 5 ml of chromosulfuric acid. Subsequently, washing with a lot of water, air-drying and heating to 50°C in 15 ml of dioxane takes place. Subsequently, 2.5 ml of a 2 molar N,N'-diisopropylethylamine solution in dioxane are added and stirred for 30 minutes. Subsequently, 2.5 ml of a 1 molar CNCI solution in dioxane are added and stirred for further 2 hours. Subsequently, washing takes place first with dioxane, then with dioxane/water and finally with pure water. The glass modified in this way is inserted into 20 ml of a solution of 1 mol/l of ethylenediamine and 0.1 moles/l of $NaHCO_3$, subsequently heated to 50°C, and stirred for 72 hours at this temperature. Subsequently, 0.1 mg of sphingoglycolipid of human erythrocytes are dissolved in 20 ml of 0.1 molar $NaHCO_3$ and stirred for 110 hours at 60°C together with the substituted glass. Subsequently, 2.5 ml of ethanolamine are added and stirred for further 30

minutes. The coated glass is washed with a 4 molar NaCl solution and subsequently washed with a lot of water and dried in the air.

7.) IMMOBILIZATION OF ERYTHROCYTE PLASMA MEMBRANE HEPARAN SULFATE ONTO THE OXIDE LAYER OF NICKEL, TITANIUM, ALUMINIUM OR SIMILAR METALS:

The metal workpiece is cleaned for four hours in an ultrasonic bath with hot water, washed with acetone and degreased for one hour in a Soxhlet extractor with chloroform. The workpiece cleaned in this way is dried and immersed into a 0.01 – 0.1 molar solution of ω-hexadecenyltrichlorosilane in bicyclohexyl for 2-15 minutes under stirring, washed two times with chloroform and water, and extracted for 15 minutes with chloroform in the Soxhlet extractor. The workpiece is immersed into a solution of 2 ml of acetone and 100 mg of $KMnO_4$ in 18 ml of water at 0°C for 45 minutes, and a CO_2 stream is passed therethrough. Subsequently, it is immersed for 15 seconds into a 20% solution of sodium bisulfite in water, washed with water and dried.

The workpiece is stirred over night in a solution of 29.25 g of paratoluyl sulfonyl chloride in 900 ml of acetone and 180 ml of pyridine at 40°C. Subsequently, the workpiece is washed with water and methanol and stirred for 40 hours at 60°C in a solution of 1 mmol/l diaminododecane in 1 liter of dimethylformamide. Subsequently, the workpiece is successively washed with water, 1 mol/l soda solution, 1 mmol/l hydrochloric acid and water. The workpiece prepared in this way is stirred for 90 minutes in a borate buffer solution (sodium tetraborate 0.065 moles/l, pH 9.5). Finally, stirring takes place over night in a solution of 0.3 g of 4-azido-1-fluoro-2-nitrobenzene in one liter of ethanol at 37°C. 0.5 g of erythrocyte plasma membrane heparan sulfate are dissolved in one liter of a 0.1 molar 2-(N-morpholino)ethane sulfone acid-(MES)-buffer pH 4.75 and stirred with the workpiece at 4°C for 48 hours. The erythrocyte plasma membrane heparan sulfate is covalently immobilized by illumination for 10 minutes by means of a high-pressure mercury lamp. After washing with a 4 molar saline solution for 40 minutes, the workpiece is washed with water and subsequently dried.

8.) PHOTOCHEMICAL IMMOBILIZATION OF LEUCOCYTE PLASMA MEMBRANE CHONDROITIN SULFATE ONTO CELLULOSE:

3 g of cellulose membrane are allowed to swell in a 4 molar NaOH for 2 hours, washed three times with water, once with water/acetone and once with acetone. The cellulose activated in this way is stirred over night in a solution of 29.25 g of paratoluyl sulfonyl chloride in 900 ml of acetone and 180 ml of pyridine at 40°C. Subsequently, the cellulose membrane is washed with water and methanol. The resulting esterified cellulose membrane is now stirred for 40 hours at 60°C in a solution of 1 mmoles/l of diaminododecane in 1 liter of dimethylformamide. Subsequently, the membrane is successively washed with water, 1 mole/l of soda solution, 1 mmol/l of hydrochloric acid and water. The amino cellulose obtained in this way is stirred for 90 minutes in a borate buffer solution (sodium tetraborate 0.065 molar, pH 9.5). Finally, the membrane is stirred in a solution of 0.3 g of 4-azido-1-fluoro-2-nitrobenzene in one liter of ethanol over night at 37°C. 0.5 g of leucocyte surface chondroitin sulfate are dissolved in one liter of a 0.1 molar 2-(N-morpholino)ethane sulfone acid buffer pH 4.75 and stirred with 2.5 g of the azido cellulose prepared as described above at 4°C for 48 hours. The leucocyte surface chondroitin sulfate is covalently immobilized by illumination for 10 minutes by means of a high-pressure mercury lamp. After washing with a 4 molar saline solution for 40 minutes and water, the cellulose membrane is dried.

9.) IMMOBILIZATION OF GLYCOPHORIN A WITH GLUTARDIALDEHYDE ONTO SILICONE:

To 1 g of silicone film, 20 ml of water and 2 ml of 3-aminopropyl triethoxy silane are added, and the pH value is set to 3.5. Subsequently, heating for 2 hours to 75°C, washing with water and drying takes place. To the resulting amino-group containing silicone, a 2.5 per cent solution of glutardialdehyde in a 0.05 molar sodium phosphate buffer is added, and it is set to pH 7. After stirring for 60 minutes at room temperature, the activated silicone produced in this way is reacted with a 0.1% solution of glycophorin A (Sigma) under stirring for 2-4 hours and is washed with water.

10.) IMMOBILIZATION OF ERYTHROCYTE PLASMA MEMBRANE HEPARAN SULFATE ONTO POLYVINYL CHLORIDE (PVC):

0.5 g of iron-II-sulfate, 100 µl of concentrated sulfuric acid and 2 ml of methacrylic acid are dissolved in 250 ml of water. 125 mg of sodium disulfite and 125 mg of potassium peroxodisulfate are added to this solution. Subsequently, the solution is pumped for 2 hours at room temperature through a ring-shaped PVC tube having a length of 1 m and an inner diameter of 3 mm. The graft polymerization taking place thereby is stopped by adding 100 mg of hydroquinone. Subsequently, the tube is thoroughly washed with water. A solution cooled to 4°C of 250 mg of CME-CDI (N-cyclohexyl-N'-2-morpholinoethyl)carbodiimide methyl tosylate in 250 ml of a 0.1 molar 2-(N-morpholino)ethane sulfone acid buffer pH 4.75 is pumped through the tube in a circle at 4°C for 30 minutes. The tube activated in this way is washed with a 0.1 molar 2-(N-morpholino)ethane sulfone acid buffer pH 4.75. Subsequently, a solution of 1 mg of erythrocyte plasma membrane heparan sulfate in a 0.1 molar 2-(N-morpholino)ethane sulfone acid buffer pH 4.75 is pumped through the tube in a circle at 4°C for 15 hours.

Finally, the tube is washed with a 4 molar saline solution and subsequently with water.

CLAIMS 1-14:

1. Hemocompatible surfaces, characterized in that they contain as materials artificial and/or natural organic and/or inorganic compounds and/or mixtures thereof and/or materials having contact with blood and/or other body fluids in invasive operations and/or animal organs and/or organ parts, and constituents of the outer layers of blood cells and/or mesothelial cells are applied and/or incorporated onto and/or into the surfaces of said materials.

2. The hemocompatible surfaces according to claim 1, characterized in that they are non-thrombogenic and/or non-immunogenic.

3. The hemocompatible surfaces according to one of claims 1 or 2, containing glycophorins on and/or in the surfaces of the materials.

4. The hemocompatible surfaces according to one of claims 1–3, containing on and/or in the surfaces of the materials oligosaccharide, polysaccharide and/or lipid portions of the glycoproteins, glycolipids and/or proteoglycans from the outer layer of blood cells and/or mesothelial cells.

5. The hemocompatible surfaces according to one of claims 1-4, containing glycosphingolipids on and/or in the surfaces of the materials.

6. The hemocompatible surfaces according to one of claims 1–5, containing on and/or in the surfaces of the materials as the oligosaccharide and/or polysaccharide portions of the proteoglycans hyaluronic acids, chondroitin sulfates, dermatan sulfates, heparan sulfates, keratan sulfates or mixtures thereof.

7. The hemocompatible surfaces according to one of claims 1–6, containing on and/or in the surfaces of the materials heparan sulfate of the erythrocyte plasma membrane of animal and/or human origin.

8. The hemocompatible surfaces according to one of claims 1–7, containing as the materials high-molecular organic compounds and/or metals, metal oxides, alloys, ceramics, glasses, minerals and/or mixtures of the materials mentioned before.

9. A process for making hemocompatible surfaces, characterized in that

a) glycophorins and/or oligosaccharide, polysaccharide and/or lipid portions of the glycoproteins, glycolipids and/or proteoglycans are isolated from the outer layer of blood cells and/or mesothelial cells, and

b) said cell constituents are applied and/or incorporated onto and/or into the surfaces of materials of artificial and/or natural organic and/or inorganic compounds and/or mixtures thereof and/or materials having contact with blood and/or other body fluids in invasive operations and/or animal organs and/or organ parts by physical or chemical bonding.

10. The process according to claim 9, characterized in that the constituents of the outer layer of blood cells are isolated from whole blood and/or from cell fractions obtained therefrom of human or animal origin.

11. The process according to one of claims 9 or 10, characterized in that cell constituents are isolated from erythrocytes, leucocytes and/or thrombocytes and/or mixtures thereof.

12. The process according to one of claims 9-11, characterized in that constituents of the outer layer of mesothelial cells are isolated from omentum, peritoneum and/or inner organs.

13. The process according to one of claims 9–12, characterized in that a chemical immobilization, photoimmobilization, adhesion, drying process or a combination thereof is carried out for applying and/or incorporating the cell constituents onto and/or into the surfaces of the materials.

14. Use of hemocompatible surfaces according to one of claims 1-8 in extensive fields of health, in medicine, dentistry, surgery, cosmetics and/or in fields having contact with blood, tissue and/or other body fluids during invasive operations.

DECLARATION AND POWER OF ATTORNEY

Attorney's Docket No. 49276-262679

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: Hemocompatible Surfaces and Process for the Production Thereof, the specification of which

☐ is attached hereto.

☒ was filed on 08/24/01 as U.S. Application or PCT International Application No. 09/914,241 and was amended (if applicable) on 8/24/01.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I do not know and do not believe that the same was ever known or used by others in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to the date of this application. I further state that the invention was not in public use or on sale in the United States of America more than one year prior to the date of this application. *I understand that I have a duty of candor and good faith toward the Patent and Trademark Office,* and I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate disclosing subject matter in common with the above-identified specification and having a filing date before that of the application on which priority is claimed:

Country	App. No.	Date of Filing	Priority Claimed Under 35 USC §119
Germany	199 08 318 5	February 26, 1999	Yes X No

I hereby claim the benefit under Title 35, United States Code, § 120 of any prior United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each claim of the present application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application No.	Filing Date	Status: patented, pending, abandoned
PCT/EP00/01497	24 February 2000	

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statement were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

I hereby authorize the U.S. attorneys named herein to accept and follow instructions from **Zimmermann & Partner,** as to any action to be taken in the Patent and Trademark Office regarding this application, without direct communication between the U.S. attorney and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney named herein will be notified by the undersigned.

POWER OF ATTORNEY: The following attorneys are hereby appointed to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: **Customer Number 23370**

Direct all correspondence to: **Customer Number 23370**

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AFFIX BAR CODE LABEL HERE →

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☒ Additional inventors are being named on separately numbered sheets attached hereto.

2-0

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